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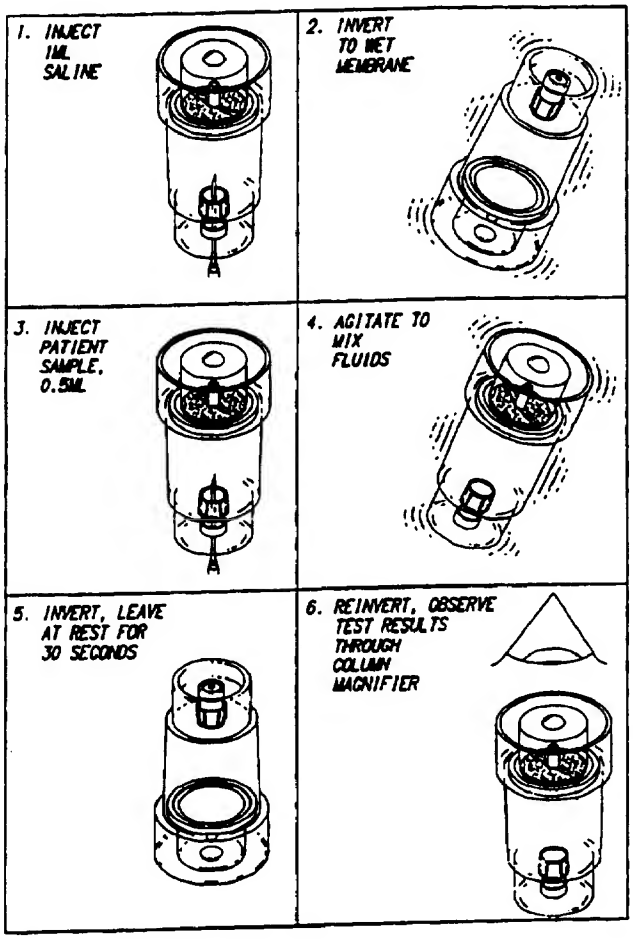
(54) Title: DISPOSABLE HEMOLYSIS DETECTOR

(57) Abstract

A method and apparatus for detecting hemolysis from a sample of a patient's blood. A sealed chamber having a fixed volume is provided for receiving the sample of blood. The sealed chamber has an internal pressure resulting form a presence of a fixed quantity of air inside the chamber. A volume of fluid that includes the sample of blood is received into the sealed chamber. While the sample is being received into the sealed chamber, the internal pressure of the sealed chamber is raised to an increased internal pressure by retaining the fixed quantity of air inside the sealed chamber as the fluid is received into the chamber. The increased internal pressure causes the plasma portion of the blood sample in the chamber to permeate a membrane that forms at least a portion of one side of the chamber. A test volume of the plasma portion of the sample is received by a hemolysis detection means after the test volume of the plasma portion has permeated the membrane, and a hemolysis condition is detected in accordance with a hue associated with the test volume received into the hemolysis detection means.



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DISPOSABLE HEMOLYSIS DETECTOR

BACKGROUND OF THE INVENTION

The present invention relates to systems and methods for detecting hemolysis in a patient's blood, and in particular, to disposable systems that may be used to detect hemolysis in non-laboratory environments. Even more particularly, the present invention relates to systems and methods that clinicians may use in a patient's room for detecting hemolysis.

During the treatment of patients by extracorporeal blood circuits during hemodialysis, hyperthermia, open-heart surgery, immunosorbent therapy, extracorporeal photochemotherapy, and blood transfusions, there is a risk that hemolysis, or the breaking of red blood cells, may occur. Such breaking of red blood cells is deleterious not only from the loss of function of those cells, but also by the release into the blood plasma of hemoglobin which is toxic.

At present, hemolysis is typically detected during extracorporeal therapies by first taking a sample of a patient's blood to a laboratory where the sample is placed in a rotating centrifuge for separating the red blood cells in the sample from the plasma, and then comparing the colors of the plasma before and after or during treatment. Hemolysis testing systems which require the use of a centrifuge and a laboratory are unsatisfactory because it is possible that hemolysis may occur to a significant degree during the time that the test itself is being performed.

In addition to a centrifuge, another known method for separating out the plasma portion of a blood sample involves the use of a microporous membrane device which allows only non-cellular elements of a blood sample to permeate a membrane. However, such microporous membrane devices typically require a relatively high shear rate of the blood sample at the surface of the membrane to prevent the cellular elements of the blood sample from clogging or plugging the membrane pores. Membrane plasma separators therefore require complicated flow systems to maintain a shear rate at the membrane surface that is both high enough to promote a good plasma flux through the membrane without any clogging of the membrane pores and also low enough to prevent damage to blood cells that are separated from the plasma by the membrane. As a result, such systems are complex, expensive, and typically require a large sample volume in order to detect hemolysis.

As described above, known membrane plasma separators require high shear rates at the membrane surface to keep blood cells away from the membrane surface and to prevent such blood cells from clogging the membrane pores. Without such high shear rates, the pores in these known membrane plasma separators will immediately become clogged by blood cells and only a very small amount of plasma will be able to permeate through the membrane before it is completely masked by blood cells. This small amount of plasma is typically just enough to wet the membrane and is insufficient for determining whether hemolysis has occurred unless a massive hemolysis has occurred in the sample.

Two examples of known microporous membrane systems for separating the plasma portion of a blood sample from

its cellular elements are shown in U.S. Patent No. 3,705,100 to Blatt et al. and U.S. Patent No. 4,191,182 to Popovich et al. As described in the paragraph immediately above, plasma separation is achieved in these systems by creating a high shear rate at the membrane surface. In addition, in order to further prevent clogging or plugging of the membrane pores by the cellular elements of the blood, these systems further include means for inducing a transmembrane pressure across the membrane surface. In order to generate the high shear rate and transmembrane pressure required at the membrane surface, these prior art systems incorporate special mechanisms for controlling the blood flow velocity and pressure at the membrane surface.

It is an object of the present invention to provide a system for detecting hemolysis in an extracorporeal circuit which can be performed quickly by a clinician in a patient or treatment room without the necessity of a laboratory.

It is a further object of the present invention to provide a system for separating a blood sample into its plasma and cellular elements which is inexpensive, and which does not require external instruments or mechanisms for controlling the velocity and flow of blood at a membrane surface.

It is a still further object of the present invention to provide a system for detecting hemolysis which requires only a small amount of a patient's plasma to permeate a membrane in order to detect whether hemolysis has occurred.

These and still other objects of the invention will become apparent upon study of the accompanying drawings and description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a perspective view of a hemolysis detector according to a preferred embodiment of the present invention.

Fig. 2 is a perspective view showing the preferred hemolysis detector of Fig. 1 in its inverted position.

Fig. 3 is a sectional view showing the preferred hemolysis detector of Fig. 2.

Fig. 4 is a perspective view of a system for collecting and channeling the plasma portion of a blood sample in accordance with a preferred embodiment of the present invention.

Fig. 5 is a top view of the system for collecting and channeling the plasma portion of a blood sample shown in Fig. 4.

Fig. 6 is a sectional view of the system for collecting and channeling the plasma portion of a blood sample shown in Fig. 5.

Fig. 7 is a diagram illustrating a preferred method for using the hemolysis detector of Fig. 1 to detect hemolysis in a patient's blood sample.

Fig. 8 is a perspective view of a hemolysis detector according to a further preferred embodiment of the present invention.

Fig. 9 is a perspective view showing the preferred hemolysis detector of Fig. 8 in its inverted position.

Fig. 10 is a sectional view showing the preferred hemolysis detector of Fig. 8.

Fig. 11 is a diagram illustrating a preferred method for using the hemolysis detector of Fig. 8 to detect hemolysis in a patient's blood sample.

Fig. 12 is a perspective view of a hemolysis detector according to a still further preferred embodiment of the present invention.

Fig. 13 is a perspective view showing the preferred hemolysis detector of Fig. 12 in its inverted position.

Fig. 14 is a sectional view showing the preferred hemolysis detector of Fig. 12.

Fig. 15 is a diagram illustrating a preferred method for using the hemolysis detector of Fig. 12 to detect hemolysis in a patient's blood sample.

Fig. 16 is a top view showing a hemolysis detector according to a still further preferred embodiment of the present invention.

Fig. 17 is a sectional view of the hemolysis detector of Fig. 16.

Fig. 18 is sectional view showing a hemolysis detector according to a still further preferred embodiment of the present invention.

Fig. 19 is sectional view showing a hemolysis detector according to yet a still further preferred embodiment of the present invention.

Fig. 20 is sectional view showing a hemolysis detector according to yet a still further preferred embodiment of the present invention.

SUMMARY OF THE INVENTION

The present invention is directed to a method and apparatus for detecting hemolysis from a sample of a patient's blood. A sealed chamber having a fixed volume is provided for receiving the sample of blood. The sealed chamber has an internal pressure resulting from a presence of a fixed quantity of air inside the chamber. A volume of fluid that includes the sample of blood is received into the sealed chamber. While the sample is being received into the sealed chamber, the internal pressure of the sealed chamber is raised to an increased internal pressure by retaining the fixed quantity of air inside the sealed chamber as the fluid is received into the chamber. The increased internal pressure causes the plasma portion of the blood sample in the chamber to permeate a membrane that forms at least a portion of one side of the chamber. A test volume of the plasma portion of the sample is received by a hemolysis detection means after the test volume of the plasma portion has permeated the membrane, and a hemolysis condition is detected in accordance with

a hue associated with the test volume received into the hemolysis detection means.

In accordance with a further aspect of the present invention, a hemolysis detector for detecting hemolysis from a sample of blood includes a sealable chamber having means for receiving a volume of fluid that includes a sample of blood into the chamber. Means for transforming the sealable chamber into a sealed chamber having an internal pressure resulting from a presence of a fixed quantity of air inside the sealed chamber are also provided. The means for receiving the volume of fluid into the chamber includes means for raising the internal pressure to an increased internal pressure as the fluid is received into the chamber by retaining the fixed quantity of air in the sealed chamber as the volume of fluid is received into the chamber. The means for transforming the sealable chamber into a sealed chamber is formed of a membrane which is permeable to a plasma portion of the sample in the sealed chamber when the internal pressure in the chamber is equivalent to the increased internal pressure. Hemolysis detection means positioned outside of the chamber for receiving a test volume of the plasma portion of the sample after it has permeated the membrane is also provided. The hemolysis detection means detects a hemolysis condition in accordance with a hue associated with the test volume of the plasma portion of the sample.

In accordance with a still further aspect of the present invention, a system for detecting a blood constituent of interest from a sample of whole blood comprises a membrane for separating a plasma portion of the sample from a cellular portion of the sample. The membrane has a first side for receiving the sample of

whole blood and a second side for passing only a plasma portion of the whole blood sample. A blood barrier is coupled to and positioned against the first side of the membrane such that the blood barrier defines a perimeter enclosing the first side of said membrane. An indicator paper that is responsive to the blood constituent of interest is also provided. The indicator paper is coupled to the membrane and positioned against the second side of the membrane. During operation of this aspect of the invention, the sample of whole blood is placed inside the perimeter and in contact with the first side of the membrane. A determination of whether the constituent of interest is present in the whole blood sample is then made by observing the hue of the indicator paper.

In accordance with yet a further aspect of the present invention, a system for detecting a blood constituent of interest from a sample of whole blood comprises a membrane for separating a plasma portion of the sample from a cellular portion of the sample of blood. The membrane has a first side for receiving the sample of whole blood and a second side for passing only the plasma portion of the sample of whole blood. A blood barrier is coupled to and positioned against the first side of the membrane such that the blood barrier defines a perimeter enclosing the first side of the membrane. An indicator paper is coupled to the membrane by a plasma channelling means that is positioned against the second side of the membrane. The indicator paper is responsive to the blood constituent of interest. During operation of this aspect of the present invention, the sample of whole blood is placed inside the perimeter and in contact with the first side of the membrane. The plasma portion of the sample is collected as it permeates the membrane and then channelled

with the channelling means to the indicator paper. A determination of whether the constituent of interest is present in the whole blood sample is then made by observing the hue of the indicator paper.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to Figs. 1-3, there are shown perspective and sectional views of a hemolysis detector 100 according to a preferred embodiment of the present invention. Hemolysis detector 100 is formed of a sealable chamber 110 having a sample injection port 120 for receiving a sample of blood into the sealed chamber. Sealable chamber 110 is preferably formed of a clear rigid plastic and has a fixed internal volume. Suitable plastics for forming sealable chamber 110 include acrylic, PVC, polycarbonate or polysulfone. Sample injection port 120 is preferably formed of latex rubber or other elastic material. Sealable chamber 110 is mounted on a chamber base 130 which is also preferably formed of a clear rigid plastic. A microporous membrane disk 140 (not shown in Fig. 1, but shown in Fig. 3) is provided at and forms the bottom end of sealable chamber 110. Microporous membrane disk 140 preferably has a pore size in the range of 0.2 to 1.2 microns, and still more preferably between 0.45 - 0.80 microns. In the preferred embodiment, membrane disk 140 is only permeable to the plasma portion of a whole blood sample and non-permeable to the cellular portion of the sample. A channelling means 150 is positioned immediately below microporous membrane disk 140. The channelling means 150 collects the plasma portion of a whole blood sample as that plasma portion permeates through the membrane disk 140 and then channels that plasma portion to a clear capillary tube 160. Hemolysis detector 100 is

preferably assembled by positioning the channelling means 150 within the chamber base 130, and then ultrasonically welding sealable chamber 110 to chamber base 130 with membrane disk 140 located in-between.

Referring now to Fig. 7, there is shown a diagram illustrating a preferred method for using hemolysis detector 100 to detect hemolysis in a patient's blood sample. As shown in Fig. 7, the process begins in step 1 by injecting a wetting solution such as saline into sealable chamber 110. The wetting solution is preferably injected into sealable chamber 110 with a syringe that has been inserted through the sample injection port 120. In step 2, hemolysis detector 100 is inverted thereby causing the wetting solution injected during step 1 to wet the membrane disk 140 positioned at the bottom of sealable chamber 110. This wetting step causes the membrane disk 140 (which was previously dry and therefore permeable to air) to become impervious to air, thereby transforming sealable chamber 110 into a sealed chamber having a fixed volume of air inside. In step 3, a sample of a patient's whole blood is injected into sealed chamber 110 through sample injection port 120. Since sample injection port 120 is made of latex or rubber, no air escapes from sealed chamber 110 during injection of the whole blood sample into the chamber.

In accordance with the preferred system for operating hemolysis detector 100, the volume of the whole blood sample injected into sealed chamber 110 in step 3 preferably corresponds to 1-10% of the fixed internal volume of sealed chamber 110. Since fluid is added to sealed chamber 110 in step 3 but no air is allowed to escape from the chamber, the internal pressure in sealable

chamber rises by approximately 8-80mm Hg as a result of the injection of the whole blood sample into the sealed chamber during this step. In a still further preferred embodiment, the volume of whole blood injected during step 3 is measured precisely such that the internal pressure in sealable chamber 110 is raised by 28-30 mm Hg when the whole blood sample is injected into the sealed chamber 110. The change in pressure that results from the injection of a whole blood sample into the sealed chamber 110 can be easily determined by solving equation (1) below for the quantity P_2:

$$P_1 * V_1 = P_2 * V_2 \qquad (1)$$

where, V_1 represents the volume of air in sealed chamber 110 prior to the injection of the whole blood sample into the chamber, P_1 represents the pressure of the air in sealed chamber 110 prior to the injection of the whole blood sample into the chamber (this will typically be the ambient air pressure), V_2 represents V_1 minus the volume of the whole blood sample injected into sealed chamber 110 during step 3, and P_2 represents the air pressure within sealed chamber 110 after the whole blood sample has been injected into the chamber.

In the preferred embodiment of detector 100, the membrane disk 140 is itself used as the means for transforming sealable chamber 110 into a sealed chamber because the membrane disk 110 (which originally was in a dry state and pervious to air) becomes impervious to air when it is wetted. In alternate embodiments, other means, such as a sealable valve or opening (not shown) positioned between the interior of chamber 110 and the cutside may be used to transform chamber 110 into a sealed state.

Referring still to Fig. 7, in step 4 of the process, hemolysis detector 100 is shaken to mix the whole blood sample injected into the sealed chamber 110 during step 3 with any wetting solution remaining in the sealed chamber 110 from step 1. Next, in step 5, hemolysis detector 100 is inverted, and the plasma portion of the whole blood sample previously injected into the chamber then permeates through membrane disk 140. The increased internal pressure generated by the injection of the whole blood sample into sealed chamber 110 in step 3 functions during step 5 as an urging force to push the plasma portion of the whole blood sample through the membrane disk 140. In the preferred embodiment, the increased internal pressure generated by the injection of the whole blood sample into sealed chamber 110 should be great enough to urge the plasma portion of the blood sample through the membrane disk 140, but not so great as to cause damage to the blood sample.

In a preferred embodiment of hemolysis detector 100, the surface area of membrane disk 140 may be on the order of 3.14 square centimeters and, in step 5 of the process of Fig. 7, 0.1 to 0.15 ml of plasma will permeate membrane disk 140. Thus, in this preferred embodiment, the ratio of plasma volume permeating the membrane to the membrane surface area is 0.318 ml/sq. cm. of membrane surface area. In alternate embodiments, the ratio of plasma volume to membrane surface area may range from 0.1 to 1.0 ml/sq. cm. of membrane surface area.

Although in the preferred embodiment, the sample injection port 120 functions to raise the internal pressure inside chamber 110 as the sample is injected into the sealed chamber by retaining a fixed quantity of air

inside the chamber as the sample is received into the chamber, in alternate embodiments other means, such as a manual pressure pump (not shown) may also be used to increase the internal pressure inside the sealed chamber 110.

As the plasma portion of the whole blood sample permeates membrane disk 140 in step 5, this plasma portion is collected by channelling means 150 and then channeled into clear capillary tube 160. In step 6, hemolysis detector 100 is inverted again and the hue or tint of the plasma in capillary tube 160 is observed either with the naked eye or with a column magnifier (not shown). If the hue of the plasma is amber, this indicates that the whole blood sample was normal. Alternatively, if the hue of the plasma is pink, this indicates that hemolysis has occurred.

Although in the preferred embodiment of detector 110, described immediately above, the clear capillary tube 160 may be used alone to detect whether hemolysis has occurred in the sample simply by observing the hue or tint of plasma in the tube, in alternate embodiments an indicator paper such as guaiac paper (described below in conjunction with detector 400) may be used to detect hemolysis from the plasma after it has permeated through the membrane disk 140.

Referring now to Figs. 4-6, there are shown perspective and sectional views of channelling means 150 for collecting and channeling the plasma portion of a blood sample in accordance with a preferred embodiment of the present invention. Channelling means 150 is formed of a plurality of interconnected v-shaped channels 152. Each

adjacent pair of channels 152 is joined at a ridge 154. Ridges 154 are positioned against membrane disk 140 when hemolysis detector 100 is in its assembled state. A collection channel 156 is coupled to each of the channels 152 and to clear capillary tube 160. During operation of hemolysis detector 100 (and, in particular, during step 5 shown in Fig. 7), plasma permeating through membrane disk 140 flows first into channels 152 and then into collection channel 156. Thereafter, the plasma in collection channel 156 flows by gravity into clear capillary tube 160.

Although in the preferred embodiment of channeling means 150, channels 152 are v-shaped, in alternate embodiments such channels may be u-shaped. In addition, in alternate embodiments, channels 152 may be coupled to capillary tube 160 through multiple collection channels. Finally, in a still further alternate embodiment (not shown), a channelling means 150 may be formed of a bowl-shaped container with capillary tube 160 coupled to the lower-most portion of the bowl, such that the bowl catches plasma as it permeates through membrane disk 140 and then channels that plasma by gravity to the capillary tube 160.

Referring now to Figs. 8-10, there are shown perspective and sectional views of a hemolysis detector 200 according to a further preferred embodiment of the present invention. Hemolysis detector 200 is substantially equivalent to hemolysis detector 100, except, as explained more fully below, hemolysis detector 200 is shaped slightly differently and has its sample injection port 220 located on the lengthwise portion of sealable chamber 210. Thus, hemolysis detector 200 is formed of a sealable chamber 210 having a sample injection port 220 for receiving a sample of blood into the sealed

chamber. Like sealable chamber 110, sealable chamber 220 is preferably formed of a clear rigid plastic and has a fixed internal volume. Sealable chamber 210 is mounted to a chamber base 230 which is also preferably formed of a clear rigid plastic. A microporous membrane disk 240 (not shown in Fig. 8, but shown in Fig. 10) is provided at and forms one end of sealable chamber 210. Microporous membrane disk 240 is substantially equivalent to membrane disk 140. A channelling means 250 is positioned immediately adjacent to microporous membrane disk 240. The channelling means 250 collects the plasma portion of a whole blood sample as that plasma portion permeates through the membrane disk 240 and then channels that plasma portion to a clear capillary tube 260.

Referring now to Fig. 11, there is shown a diagram illustrating a preferred method for using hemolysis detector 200 to detect hemolysis in a patient's blood sample. As shown in Fig. 11, hemolysis detector 200 is used in substantially the same manner as hemolysis detector 100, except that in hemolysis detector 200 the injection of the saline solution and whole blood sample in steps 1 and 3 is accomplished using a sample injection port positioned along the lengthwise portion of chamber 210.

Referring now to Figs. 12-14, there are shown perspective and sectional views of a hemolysis detector 300 according to a still further preferred embodiment of the present invention. Hemolysis detector 300 is formed of a sealable chamber 310 having a sample injection port 320 for receiving a sample of blood into the sealed chamber. Sealable chamber 310 is preferably formed of a clear rigid plastic and has a fixed internal volume. A

capillary tube cover 330 is secured to sealable chamber 310. Capillary tube cover 330 is also preferably formed of a clear rigid plastic. A microporous membrane disk 340 (not shown in Figs. 12-13, but shown in Fig. 14) is provided at and forms a boundary defining one wall of sealable chamber 310. Thus, in contrast to the systems of hemolysis detectors 100 and 200 which were formed of sealable chambers that were cylindrical in shape, hemolysis detector 300 is formed of a sealable chamber 310 that is essentially L-shaped. For purposes of clarity, the internal portion of hemolysis detector 300 occupied by sealable chamber 310 is indicated in Fig. 14 by parallel line shading. As was the case in hemolysis detectors 100 and 200, the microporous membrane disk 340 in hemolysis detector 300 preferably has a pore size in the range of 0.2 to 1.2 microns, and still more preferably between 0.45 - 0.80 microns, and is only permeable to the plasma portion of a whole blood sample and non-permeable to the cellular portion of the sample. A channelling means 350 is positioned immediately adjacent to microporous membrane disk 340. The channelling means 350 collects the plasma portion of a whole blood sample as that plasma portion permeates through the membrane disk 340 and then channels that plasma portion to a clear capillary tube 360. Hemolysis detector 300 is preferably assembled by positioning the channelling means 350 within the capillary tube cover 330, and then ultrasonically welding sealable chamber 310 to the cover 330 with membrane disk 340 located in-between.

Referring now to Fig. 15, there is shown a diagram illustrating a preferred method for using hemolysis detector 300 to detect hemolysis in a patient's blood sample. As shown in Fig. 15, the process begins in step

1 by injecting a wetting solution such as saline into sealable chamber 310 through the sample injection port 320. In step 2, hemolysis detector 300 is tipped sideways and agitated, thereby causing the wetting solution injected during step 1 to wet the membrane disk 340. This wetting step causes the membrane disk 340 (which was previously dry and therefore permeable to air) to become impervious to air, thereby transforming sealable chamber 310 into a sealed chamber having a fixed volume of air inside. In step 3, a sample of a patient's whole blood is injected into sealed chamber 310 through sample injection port 320. Since sample injection port 320 is made of latex or rubber, no air escapes from sealed chamber 310 during injection of the whole blood sample into the chamber. The volume of the whole blood sample injected into sealed chamber 310 in step 3 preferably corresponds to 1-10% of the fixed internal volume of sealed chamber 310. As discussed above in connection with hemolysis detector 100, the addition of this fluid into the sealed chamber causes its internal pressure to rise by approximately 8-80mm Hg, and preferably by 28-30 mm Hg.

Referring still to Fig. 15, in step 4 of the process, hemolysis detector 300 is shaken to mix the whole blood sample injected into the sealed chamber 310 during step 3 with any wetting solution remaining in the sealed chamber 310 from step 1. Next, in step 5, hemolysis detector 300 is inverted, and the plasma portion of the whole blood sample previously injected into the chamber then permeates through membrane disk 340. The increased internal pressure generated by the injection of the whole blood sample into sealed chamber 310 in step 3 and the downward pressure created by the weight of the whole blood sample itself together function during step 5 as an urging force

to push the plasma portion of the whole blood sample in an upward direction through the membrane disk 340. As the plasma portion of the whole blood sample permeates membrane disk 340 in step 5, this plasma portion is collected by channelling means 350 and then channeled in an upward direction into clear capillary tube 360. In step 6, the hue or tint of the plasma in capillary tube 360 is observed either with the naked eye or with a column magnifier (not shown). If the hue of the plasma is amber, this indicates that the whole blood sample was normal. Alternatively, if the hue of the plasma is pink, this indicates that hemolysis has occurred.

Referring now to Fig. 17, there is shown a sectional view of a hemolysis detector 400 according to a still further preferred embodiment of the present invention. Hemolysis detector 400 is formed of a microporous membrane disk 410 for separating the plasma portion of a sample of whole blood from the cellular portion of the whole blood sample. Membrane disk 410 has a first side 420 for receiving the sample of whole blood to be separated. In the embodiment shown in Fig. 17, the whole blood sample is preferably received onto membrane disk 410 by placing one or more drops of the whole blood sample onto the first side 420 of membrane disk 410. Microporous membrane disk 410 preferably has a pore size in the range of 0.2 to 1.2 microns, and still more preferably between 0.45 - 0.80 microns. Since membrane disk 410 is only permeable to the plasma portion of a whole blood sample and non-permeable to the cellular portion of the sample, only plasma from the whole blood sample placed on first side 420 will pass through to the second side 430 of membrane disk 410.

Membrane disk 410 is preferably formed from of a hydrophilic membrane such as Thermopor 800, Verapor 800, or Supor 800 made by Gelman Science, Inc. It will be understood by those skilled in the art that other microporous membranes, including hydrophobic membranes that require a pre-wetting step, could be used to form membrane disk 410. In addition, in the preferred embodiment membrane disk 410 is 5 - 10 mm in diameter, although disks having larger or smaller diameters could also be used. It will also be understood by those skilled in the art that membranes formed in shapes other than disks could also be used in place of membrane disk 410.

A blood barrier 440 is coupled to and positioned against the first side 420 of membrane disk 410. Blood barrier 440 is preferably circular in shape and defines a perimeter 450 enclosing the first side 420 of membrane disk 410. In the preferred embodiment, membrane disk 410 and blood barrier 440 are glued together, although these elements could be secured to each other using other means of attachment. Blood barrier 440 is preferably formed of a molded plastic material.

Referring still to Figs. 16 and 17, hemolysis detector 400 is further formed of an indicator paper disk 460 which is secured inside a plastic casing 470 by glue 480 or by other attachment means. Indicator paper disk 460 is preferably positioned directly adjacent to and in contact with the second side 430 of membrane disk 410. Indicator paper disk 460 is also preferably coupled to membrane disk 410 in a detachable manner so that indicator disk 460 and membrane disk 410 can be easily separated. Indicator paper disk 460 is preferably formed of a porous paper impregnated with guaiac resin such as Hemoccult

paper manufactured by SmithKline Diagnostics, Inc. Such paper displays a blue color in the presence of hemoglobin when treated with a hydrogen peroxide solution. A suitable hydrogen peroxide solution for use in conjunction with this aspect of the present invention is the Hemoccult Developer manufactured by SmithKline Diagnostics, Inc.

Indicator paper disk 460 preferably has a larger diameter than membrane disk 410 and, in the embodiment shown, is approximately 20mm in diameter. Since in the preferred embodiment indicator paper disk 460 is larger than membrane disk 410, a portion of indicator paper disk 460 will lie outside of perimeter 450. It will, however, be understood by those skilled in the art that indicator paper formed in shapes other than disks could also be used in place of disk 460.

To test for the presence of free hemoglobin in a sample of whole blood using hemolysis detector 400, one or more drops of a whole blood sample is placed within perimeter 450 on the first side 420 of membrane disk 410. If membrane disk 410 is formed of a hydrophobic or slightly hydrophilic paper, membrane disk 410 should be pre-wetted with a wetting solution such as an aqueous solution of 5-20% isopropyl alcohol or ethyl alcohol prior to dropping the whole blood sample onto the membrane disk 410. Other organic solvents can also be used as a wetting agent, so long as these solvents do not leave a residue in membrane disk 410 that could interfere with the blood test. The purpose of this pre-wetting step is to hydrophilize the membrane disk. The pre-wetting step can be accomplished by simply dropping one or more drops of the wetting solution onto the membrane disk 410.

After one or more drops of a whole blood sample is placed within perimeter 450 on the first side 420 of membrane disk 410, the plasma portion of the whole blood sample will wet the membrane disk 410 as well as the indicator paper disk 460 lying beneath the membrane disk 410. If the wetting of the indicator paper disk 460 propagates beyond perimeter 450, a drop of developer solution is applied to the wetted portion of the indicator paper disk 460 lying outside of perimeter 450. If blue color appears in the wetted area after approximately one minute, this is an indication of free hemoglobin in the plasma and hemolysis is therefore detected as being present. Alternatively, if the wetting of the indicator paper disk 460 does not propagate beyond perimeter 450, membrane disk 410 should be removed from its position above the indicator paper disk 460 and a drop of developer solution should then be applied to the wetted portion of the indicator paper disk 460 previously lying below membrane disk 410. Again, if blue color appears in the wetted area after approximately one minute, this is an indication of free hemoglobin in the plasma and hemolysis is therefore detected as being present.

Although in the embodiment of detector 400 described immediately above, the blood constituent of interest is free hemoglobin and an indicator paper impregnated with guaiac resin is used to detect such hemoglobin, it will be understood by those skilled in the art that detector 400 of the present invention could be applied to detect other blood constituents in plasma by varying the type of indicator paper used to form disk 460.

Referring now to Fig. 18, there is shown a sectional view of a hemolysis detector 500 according to a still

further preferred embodiment of the present invention. Hemolysis detector 500 is formed of chamber 510 which is enclosed on all sides except its bottom-most side 520. At the top of chamber 510, a sample injection port 530 is provided for receiving a whole blood sample into chamber 510. A chamber base 540 is also provided. Both chamber 510 and chamber base 540 are preferably formed from molded plastic. A microporous membrane disk 550 and an indicator paper disk 560 are also provided. Membrane disk 550 is preferably formed from of a hydrophilic membrane such as Thermopor 800, Verapor 800, or Supor 800 made by Gelman Science, Inc. It will be understood by those skilled in the art that other microporous membranes, including hydrophobic membranes can also be used. Similarly, indicator paper disk 560 is preferably formed of a porous paper impregnated with guaiac resin such as Hemoccult paper manufactured by SmithKline Diagnostics, Inc. In contrast to the system of detector 400, membrane disk 550 and indicator paper disk 560 in detector 500 have substantially the same diameter.

During assembly of detector 500, membrane disk 550 and indicator disk 560 are positioned between the top edge 570 of chamber base 540 and the bottom-most side 520 of chamber 510, and the top edge 570 of chamber base 540 and the bottom-most side 520 of chamber 510 are secured to each other with both disks in between, preferably by ultrasonic welding. Once detector 500 is assembled, the preferred application of the device begins with the injection of one or two milliliters of a wetting agent (such as 15% isopropyl alcohol in water) into the chamber 510 through the sample injection port 530. The injected wetting solution wets both the membrane disk 550 and the indicator paper disk 560, and most of the injection

solution permeates out of the device within a minute. Next, a predetermined volume of a whole blood sample (preferably 1-10% of the internal volume of chamber 510) is injected into chamber 510 through sample injection port 530. After maintaining detector 500 in its upright position with sample injection port 530 at the top for approximately one minute, detector 500 is next inverted 180 degrees and one or two drops of developer solution are applied to the indicator paper disk 560. The bottom of chamber base 540 is preferably open or exposed to the outside so as to allow the developer to be applied directly onto the indicator paper. If blue color appears in the area of the developer solution within approximately 30 seconds, this is an indication of free hemoglobin in the plasma and hemolysis is therefore detected as being present.

Although in the embodiment of detector 500 described immediately above, the blood constituent of interest is free hemoglobin and an indicator paper impregnated with guaiac resin is used to detect such hemoglobin, it will be understood by those skilled in the art that detector 500 of the present invention could be applied to detect other blood constituents in plasma by varying the type of indicator paper used to form disk 560.

Referring now to Fig. 19, there is shown a sectional view of a hemolysis detector 600 according to yet a still further preferred embodiment of the present invention. Hemolysis detector 600 is formed of chamber 610 which is enclosed on all sides except its bottom-most side 620. At the top of chamber 610, a sample injection port 630 is provided for receiving a whole blood sample into chamber 610. A chamber base 640 is also provided. Both chamber

610 and chamber base 640 are preferably formed from molded plastic. A microporous membrane disk 650 is also provided. Membrane disk 650 is the substantial equivalent of membrane disk 550 described above.

During assembly of detector 600, membrane disk 650 is positioned between the top edge 660 of chamber base 640 and the bottom-most side 620 of chamber 610, and the top edge 660 of chamber base 640 and the bottom-most side 620 of chamber 610 are secured to each other with the membrane disk in between, preferably by ultrasonic welding. Once detector 600 is assembled, the preferred application of the device begins with the injection of one or two milliliters of a wetting agent (such as a normal saline or 15% isopropyl alcohol in water) into the chamber 610 through the sample injection port 630. The injected wetting solution wets the membrane disk 650, and most of the injection solution permeates out of the device within a minute. Next, a predetermined volume of a whole blood sample (preferably 1-10% of the internal volume of chamber 610) is injected into chamber 610 through sample injection port 630. After maintaining detector 600 in its upright position with sample injection port 630 at the top for approximately one minute, detector 600 is next inverted 180 degrees and a strip of indicator paper (such as guaiac paper) is wetted by bringing the indicator paper (not shown) into contact with side 670 of membrane disk 650. The bottom of chamber base 640 is preferably open or exposed to the outside so as to allow the indicator paper to be brought into direct contact with the membrane disk. One or two drops of developer solution are next applied to the indicator paper strip. If blue color appears in the area of the developer solution within approximately 30 seconds, this is an indication of free hemoglobin in the

plasma and hemolysis is therefore detected as being present.

Although in the embodiment of detector 600 described immediately above, the blood constituent of interest is free hemoglobin and an indicator paper impregnated with guaiac resin is used to detect such hemoglobin, it will be understood by those skilled in the art that detector 600 of the present invention could be applied to detect other blood constituents in plasma by varying the type of indicator paper used during operation of the system.

Referring now to Fig. 20, there is shown a sectional view of a hemolysis detector 700 according to yet a still further preferred embodiment of the present invention. Hemolysis detector 700 is formed of chamber 710. At the top of chamber 710, a sample injection port 720 is provided for receiving a whole blood sample into chamber 710. A chamber base 730 is also provided. Both chamber 710 and chamber base 730 are preferably formed from molded plastic. A microporous membrane disk 740 is also provided on the bottom-most side of chamber 710. Membrane disk 740 is the substantial equivalent of membrane disk 550 described above. A channelling means 750 is positioned immediately below microporous membrane disk 740. Channelling means 750 is substantially equivalent to channeling means 150, and thus collects the plasma portion of a whole blood sample as that plasma portion permeates through the membrane disk 740 and then channels that plasma portion to a clear capillary tube 760. In contrast to hemolysis detector 100 wherein the bottom end of capillary tube 160 is closed, in hemolysis detector 700 the bottom end 770 of capillary tube 760 is open.

During assembly of detector 700, membrane disk 740 and channelling means 750 are positioned between the chamber base 730 and the chamber 710, and the chamber base 730 and the chamber 710 are secured to each other with the membrane disk and channeling means in between, preferably by ultrasonic welding. Once detector 700 is assembled, the preferred application of the device begins with the injection of one or two milliliters of a wetting agent (such as a normal saline or 15% isopropyl alcohol in water) into the chamber 710 through the sample injection port 720. The injected wetting solution wets the membrane disk 740, and most of the injection solution permeates out of the device within a minute. Next, a predetermined volume of a whole blood sample is injected into chamber 710 through sample injection port 720. After maintaining detector 700 in its upright position with sample injection port 720 at the top for approximately one minute, a strip of indicator paper (such as guaiac paper) is wetted by dropping plasma exiting from end 770 of tube 760 onto an indicator paper strip such as guaiac paper (not shown). One or two drops of developer solution are next applied to the indicator paper strip. If blue color appears in the area of the developer solution within approximately 30 seconds, this is an indication of free hemoglobin in the plasma and hemolysis is therefore detected as being present.

Although in the preferred embodiment of detector 700, an indicator paper is applied to plasma exiting tube 760 to determine whether hemolysis is present, it will be understood by those skilled in the art that an optical sensor system (formed of a light transmitting source 780 and a light sensor 790) may alternatively be used to

analyze the plasma from tube 760 in order to determine whether hemolysis has occurred.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes of the invention. Accordingly, reference should be made to the appended claims, rather than the foregoing specification, as indicating the scope of the invention.

What Is Claimed Is:

1. An apparatus for detecting hemolysis from a sample of blood, comprising:

(A) a sealed chamber having an internal pressure resulting from a presence of a quantity of air inside said sealed chamber;

(B) said sealed chamber having means for receiving a volume of fluid into said sealed chamber, said volume of fluid including said sample of blood, said means for receiving said volume of fluid including means for raising said internal pressure to an increased internal pressure as said fluid is received into said sealed chamber by retaining said quantity of air in said sealed chamber as said volume of fluid is received into said sealed chamber;

(C) a membrane for forming at least a portion of one side of said sealed chamber, said membrane being permeable to a plasma portion of said sample in said sealed chamber when said internal pressure is equivalent to said increased internal pressure, said membrane being impermeable to blood cells in said sample;

(D) hemolysis detection means positioned outside of said sealed chamber for receiving a test volume of said plasma portion of said sample after said test volume of said plasma has permeated said membrane, and for detecting a hemolysis condition in accordance with a hue associated with said test volume of said plasma portion.

2. The apparatus of claim 1, wherein said volume of fluid includes only said sample of blood.

3. The apparatus of claim 1, wherein said sealed chamber has a volume, and wherein said sample of blood has a volume equivalent to 1-10% of said volume of said sealed chamber.

4. The apparatus of claim 1, wherein said hemolysis detection means detects said hemolysis condition only if said hue associated with said test volume of said plasma portion is represented by a predetermined color.

5. The apparatus of claim 4, wherein said hemolysis detection means is formed of a translucent hollow tube and said hue associated with said test volume of said plasma portion is a tint appearing inside said translucent hollow tube when said test volume of said plasma portion is positioned inside said translucent hollow tube.

6. The apparatus of claim 4, wherein said hemolysis detection means is formed of an indicator paper.

7. The apparatus of claim 1, wherein said hemolysis detection means is formed of an optical sensor.

8. An apparatus for detecting hemolysis from a sample of blood, comprising:

(A) a sealable chamber, said sealable chamber having means for receiving a volume of fluid into said chamber, said volume of fluid including said sample of blood;

(B) means for transforming said sealable chamber into a sealed chamber having an internal pressure resulting from a presence of a quantity of air inside said sealed chamber;

(C) said means for receiving said volume of fluid into said chamber including means for raising said internal pressure to an increased internal pressure as said fluid is received into said chamber by retaining said quantity of air in said sealed chamber as said volume of fluid is received into said sealed chamber;

(D) said means for transforming said sealable chamber to a sealed chamber being formed of a membrane, said membrane being permeable to a plasma portion of said sample in said sealed chamber when said internal pressure is equivalent to said increased internal pressure;

(E) hemolysis detection means positioned outside of said chamber for receiving a test volume of said plasma portion of said sample after said test volume of said plasma has permeated said membrane, and for detecting a hemolysis condition in accordance with a hue associated with said test volume of said plasma portion.

9. The apparatus of claim 8, wherein said volume of fluid includes only said sample of blood.

10. The apparatus of claim 8, wherein said sealed chamber has a volume, and wherein said sample of blood has a volume equivalent to 1-10% of said volume of said sealed chamber.

11. The apparatus of claim 8, wherein said hemolysis detection means detects said hemolysis condition only if said hue associated with said test volume of said plasma portion is represented by a predetermined color.

12. The apparatus of claim 11, wherein said hemolysis detection means is formed of a translucent hollow tube and said hue associated with said test volume of said plasma portion is a tint appearing inside said translucent hollow tube when said test volume of said plasma portion is positioned inside said translucent hollow tube.

13. The apparatus of claim 8, wherein said hemolysis detection means is formed of an indicator paper.

14. The apparatus of claim 8, wherein said hemolysis detection means is formed of an optical sensor.

15. The apparatus of claim 8, wherein said membrane is adapted to convert said sealable chamber to a sealed chamber when said membrane is wetted with a wetting solution.

16. A method for detecting hemolysis from a sample of blood, comprising the steps of:

(A) providing a sealed chamber for receiving said sample of blood, said sealed chamber having an internal pressure resulting from a presence of a quantity of air inside said sealed chamber;

(B) receiving a volume of fluid into said sealed chamber, said volume of fluid including said sample of blood;

(C) raising, during said receiving step, said internal pressure to an increased internal pressure by

retaining said quantity of air in said sealed chamber as said volume of fluid is received into said sealed chamber;

(D) urging, with said increased internal pressure, a plasma portion of said sample in said sealed chamber to permeate a membrane, said membrane forming at least a portion of one side of said sealed chamber;

(E) receiving a test volume of said plasma portion of said sample in a hemolysis detection means after said test volume of said plasma portion has permeated said membrane; and

(F) detecting a hemolysis condition in accordance with a hue associated with said test volume received into said hemolysis detection means.

17. The method of claim 16, wherein step (A) comprises the steps of:

(1) providing a sealable chamber for receiving said sample of blood; and

(2) transforming said sealable chamber into a sealed chamber by applying a wetting solution to said membrane, said sealed chamber having an internal pressure resulting from a presence of a quantity of air inside said sealed chamber.

18. The method of claim 16, wherein said volume of fluid includes only said sample of blood.

19. The method of claim 16, wherein said sealed chamber has a volume, and wherein said sample of blood has

a volume equivalent to 1-10% of said volume of said sealed chamber.

20. The method of claim 16, wherein said hemolysis condition is detected in step (F) only if said hue associated with said test volume of said plasma portion is represented by a predetermined color.

21. The method of claim 20, wherein said hemolysis detection means is formed of a translucent hollow tube and wherein said hemolysis condition is detected in step (F) only by observing a tint appearing inside said translucent hollow tube when said test volume of said plasma portion is positioned inside said translucent hollow tube.

22. The method of claim 20, wherein said hemolysis detection means is formed of an indicator paper and wherein said hemolysis condition is detected in step (F) by applying at least one drop of said test volume of said plasma portion to said indicator paper and observing a tint appearing on said indicator paper.

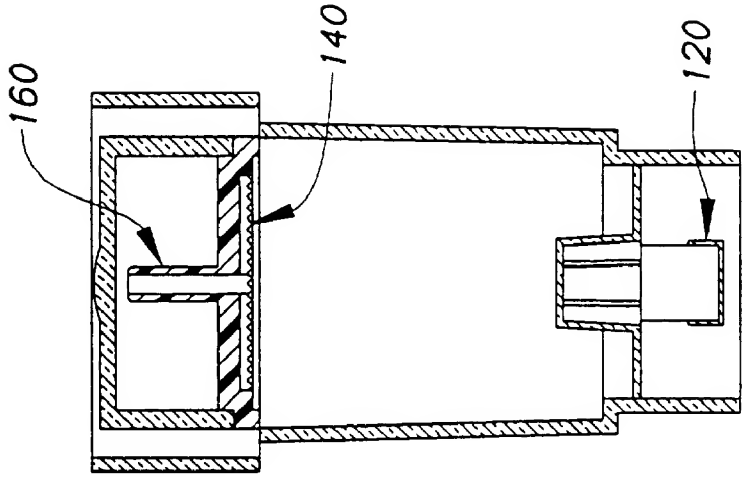


FIG. 3

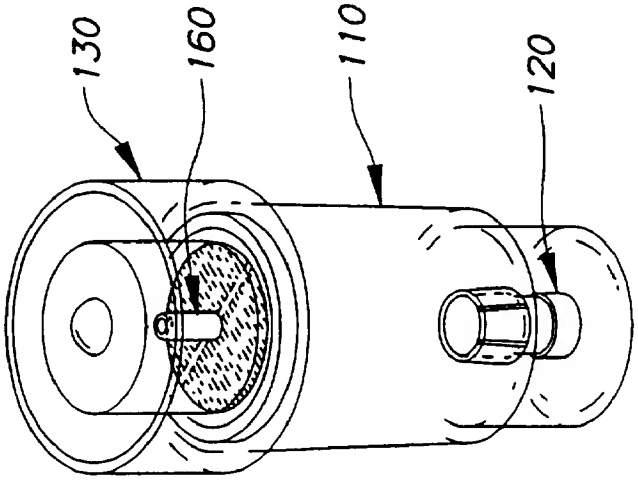


FIG. 2

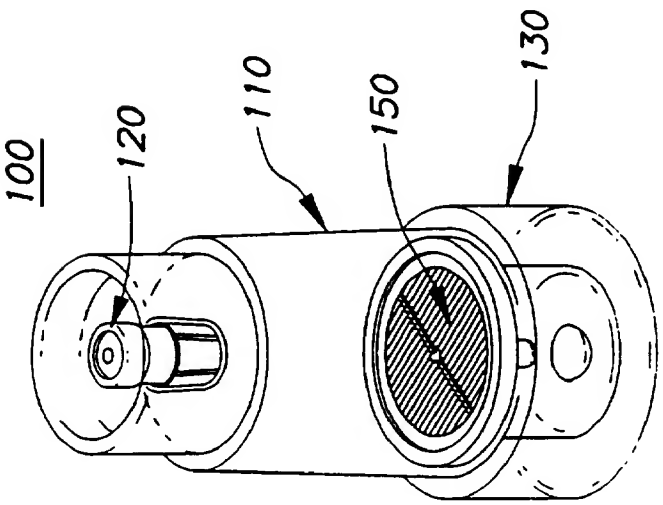


FIG. 1

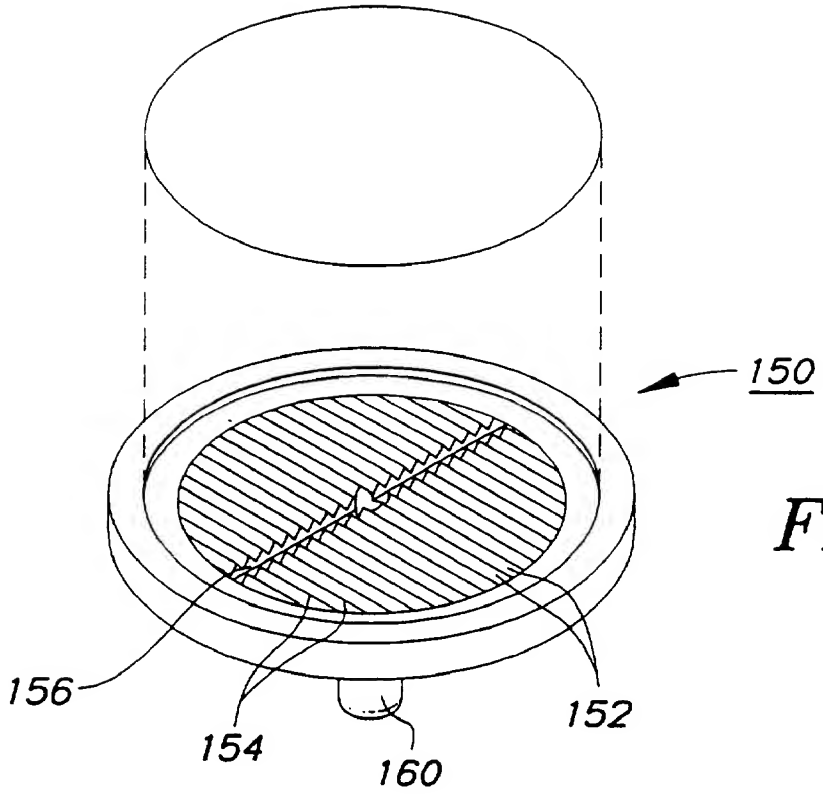


FIG. 4

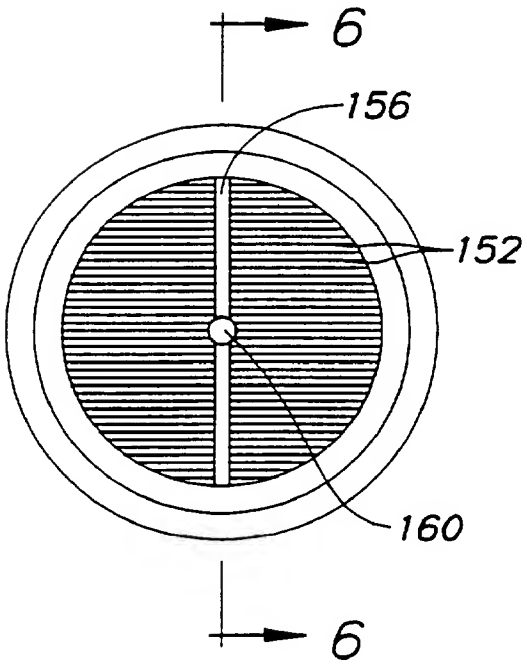


FIG. 5

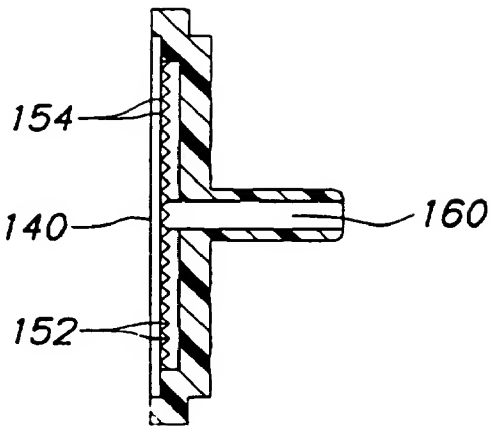
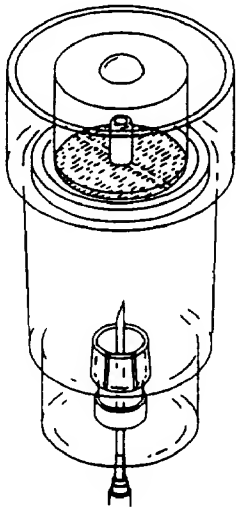


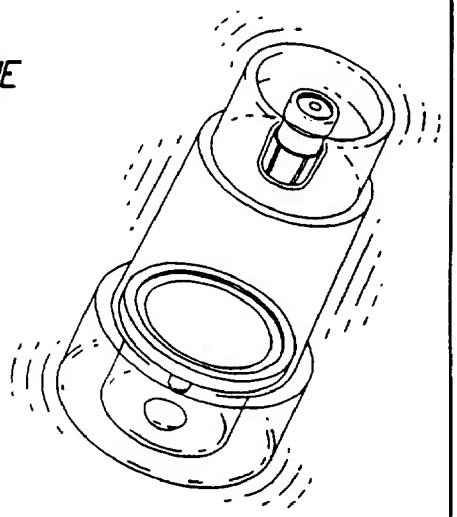
FIG. 6

FIG. 7

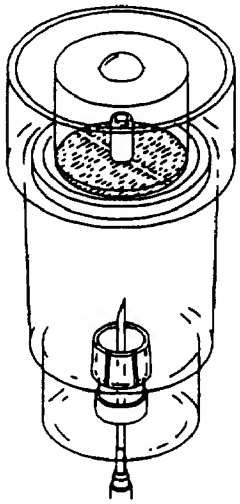
1. INJECT 1ML SALINE



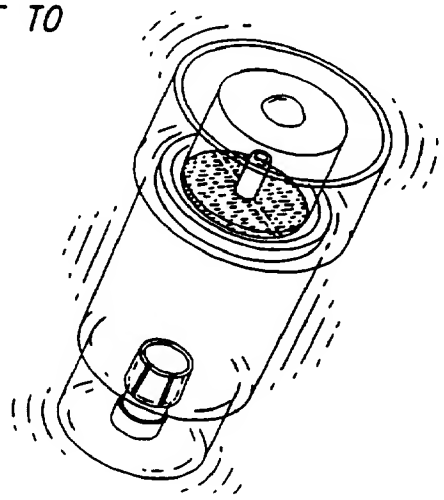
2. INVERT TO WET MEMBRANE



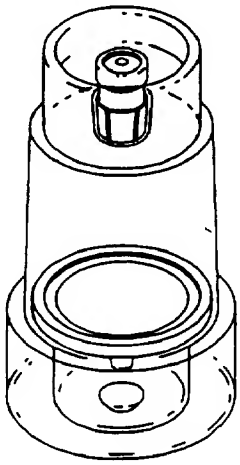
3. INJECT PATIENT SAMPLE, 0.5ML



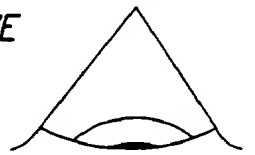
4. AGITATE TO MIX FLUIDS

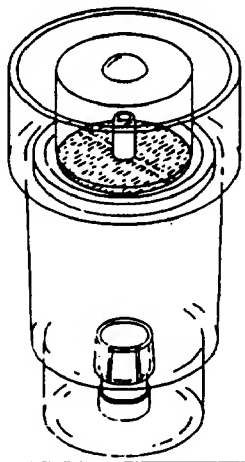


5. INVERT, LEAVE AT REST FOR 30 SECONDS



6. REINVERT, OBSERVE TEST RESULTS THROUGH COLUMN MAGNIFIER





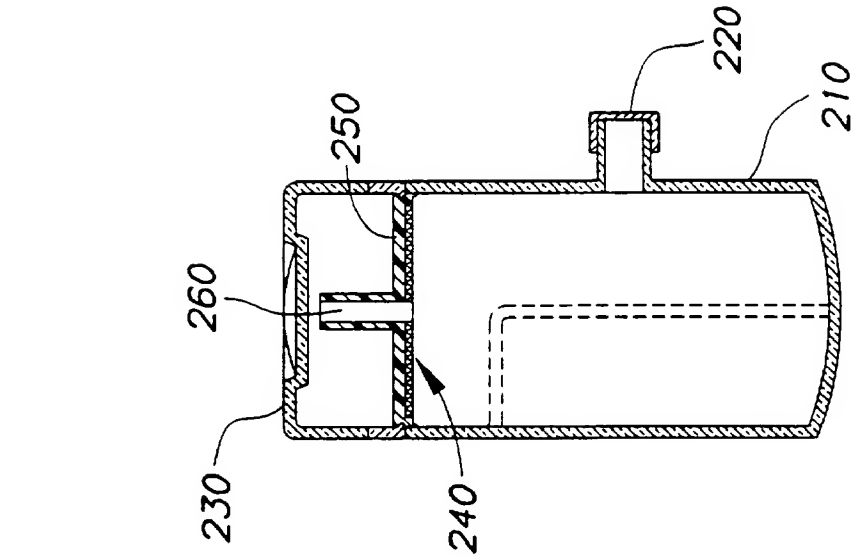


FIG. 10

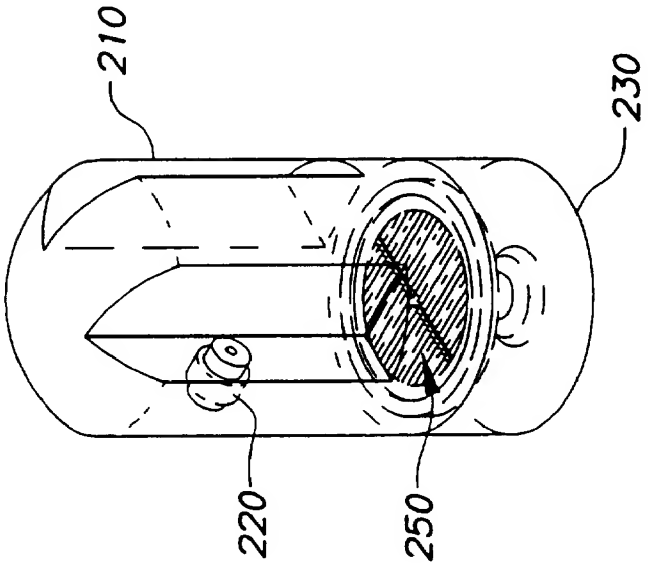


FIG. 9

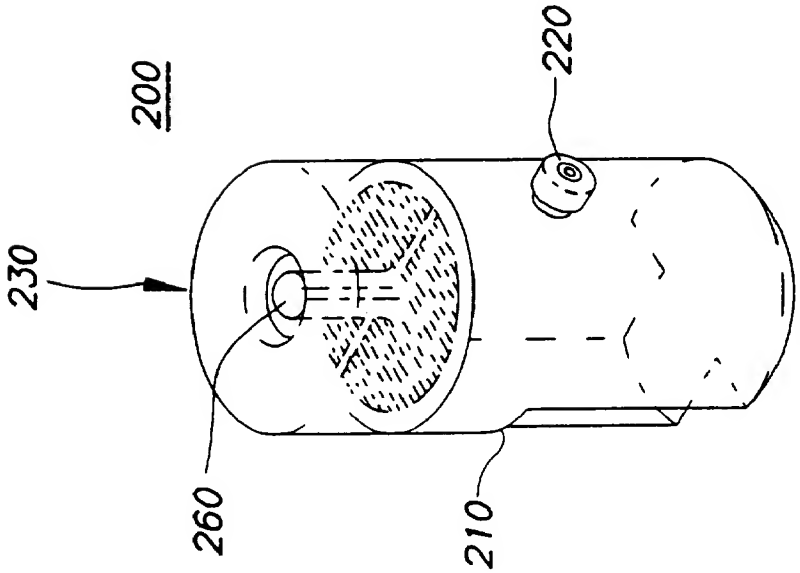
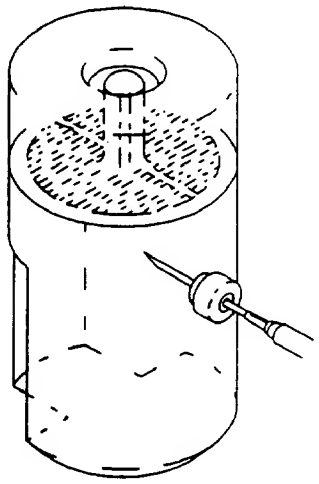


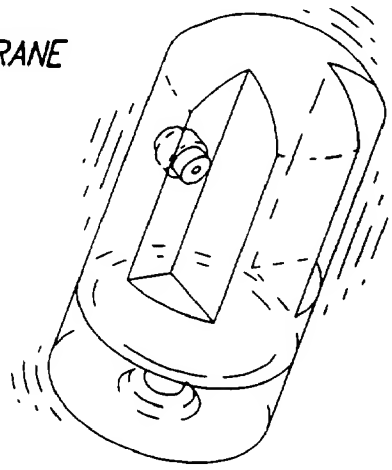
FIG. 8

FIG. 11

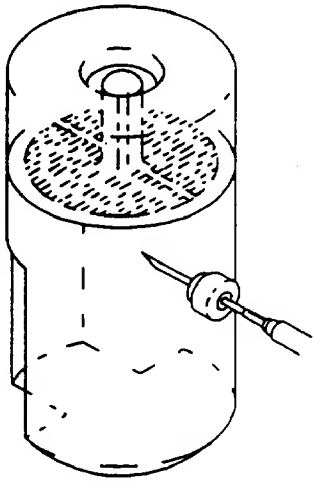
1. INJECT 1ML SALINE



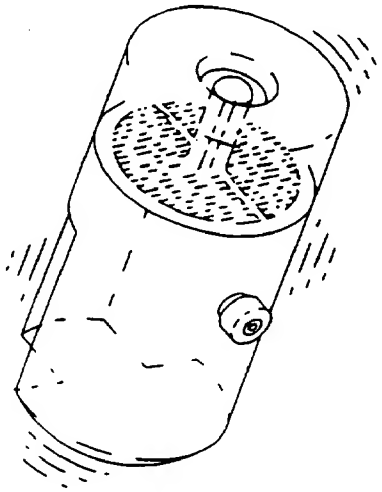
2. INVERT TO WET MEMBRANE



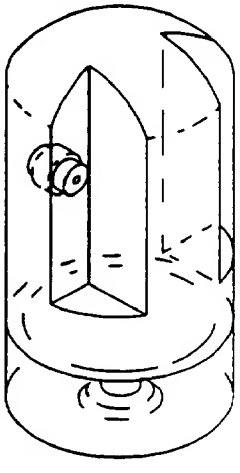
3. INJECT PATIENT SAMPLE, 0.5ML



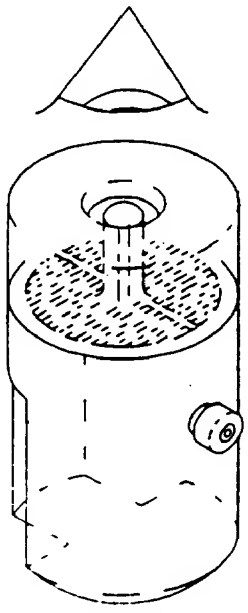
4. AGITATE TO MIX FLUIDS



5. INVERT, LEAVE AT REST FOR 30 SECONDS



6. REINVERT, OBSERVE TEST RESULTS THROUGH COLUMN MAGNIFIER



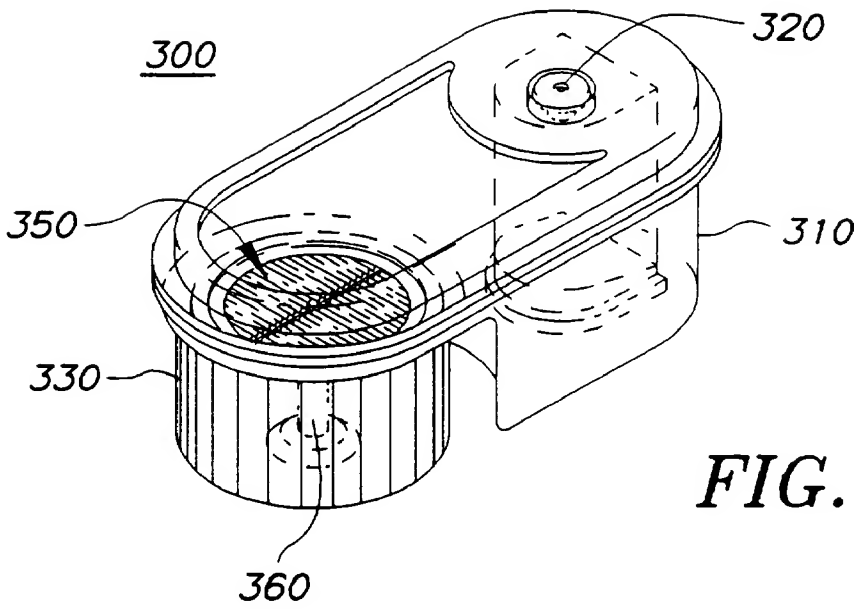


FIG. 12

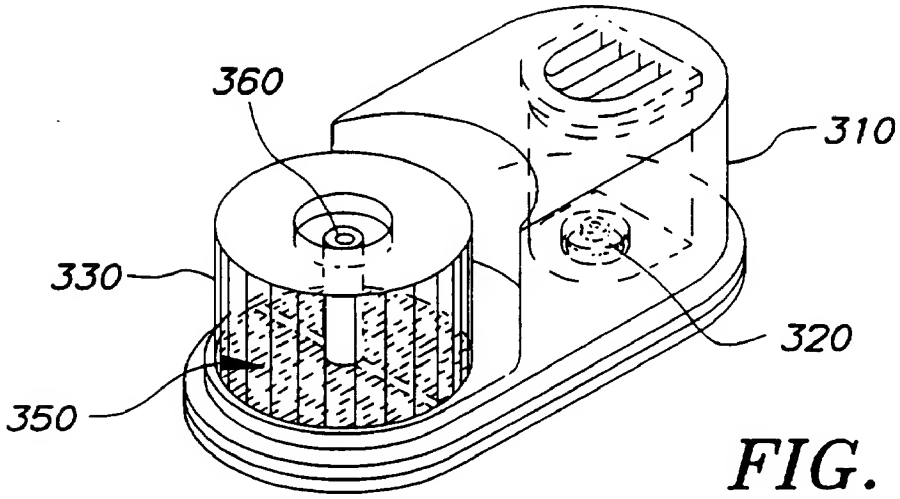


FIG. 13

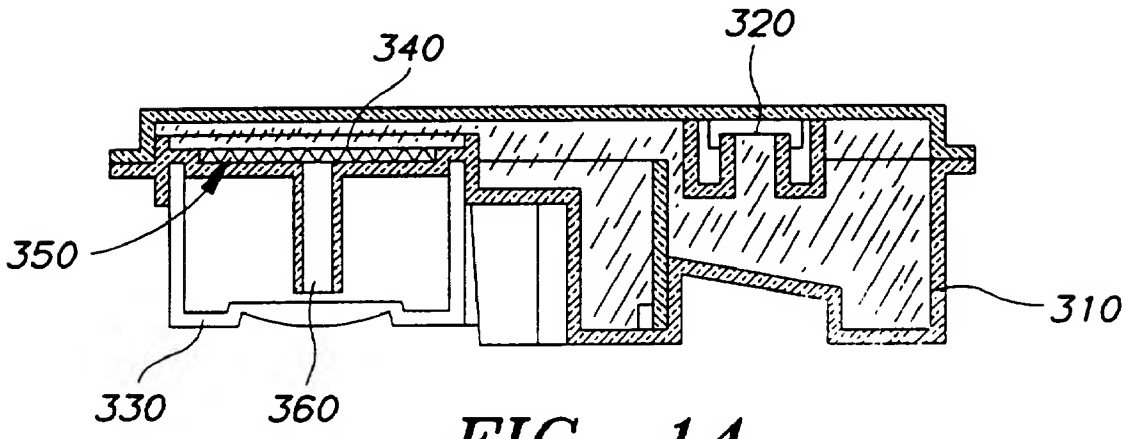


FIG. 14

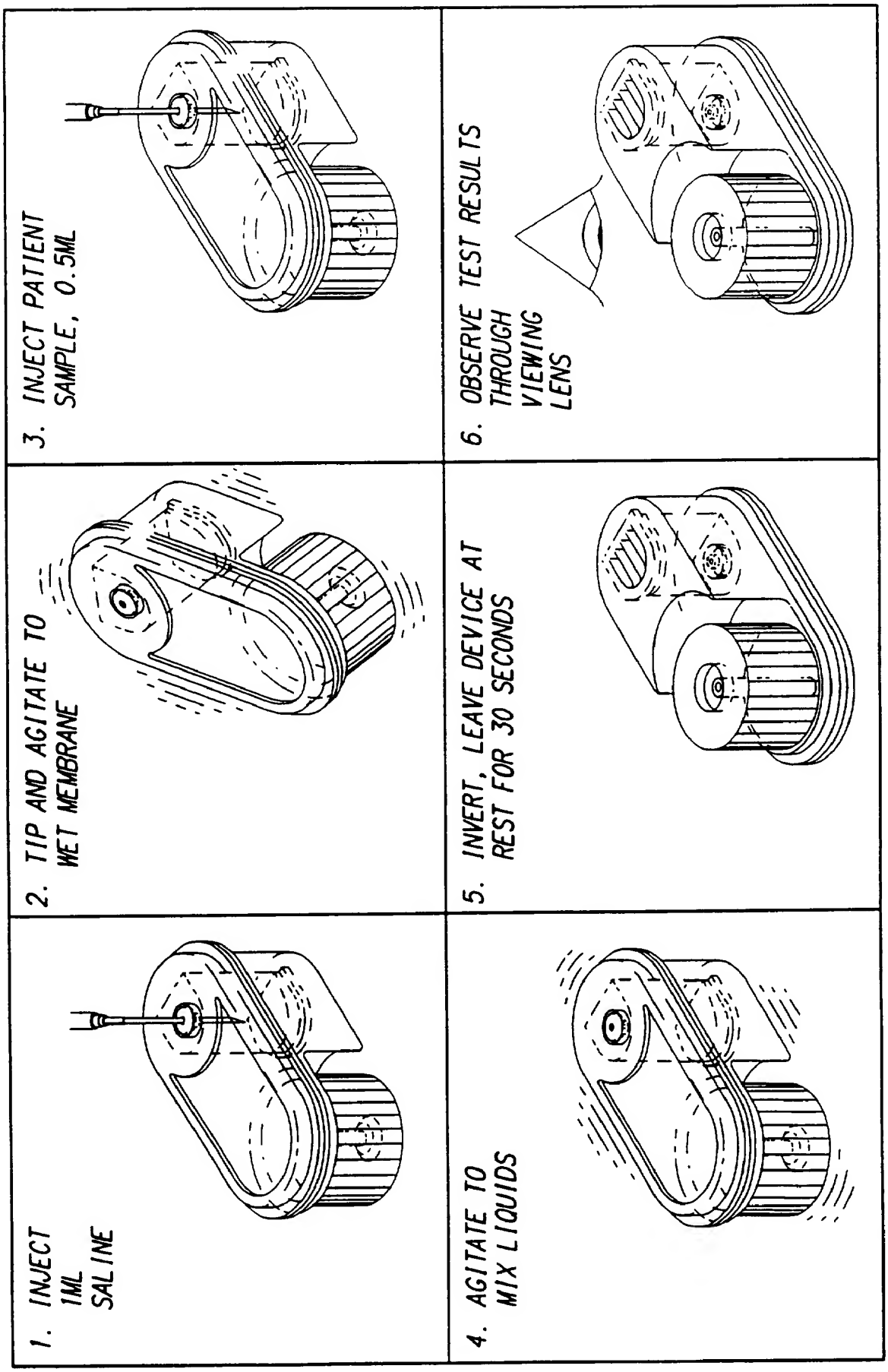

1. INJECT 1ML SALINE
2. TIP AND AGITATE TO WET MEMBRANE
3. INJECT PATIENT SAMPLE, 0.5ML
4. AGITATE TO MIX LIQUIDS
5. INVERT, LEAVE DEVICE AT REST FOR 30 SECONDS
6. OBSERVE TEST RESULTS THROUGH VIEWING LENS

FIG. 15

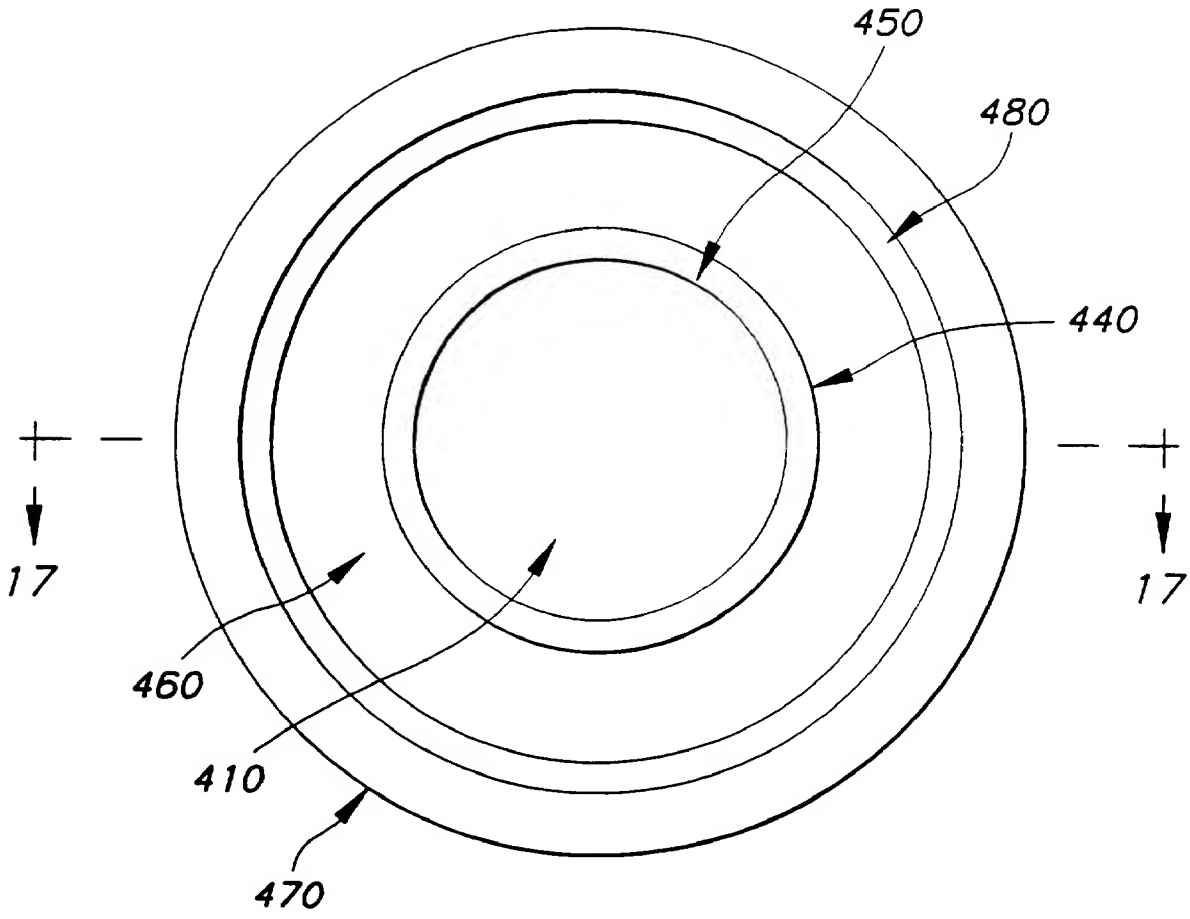


FIG. 16

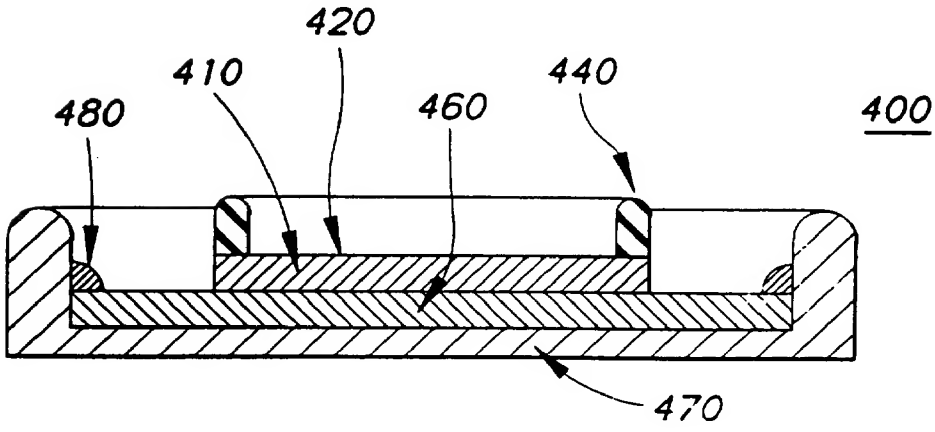


FIG. 17

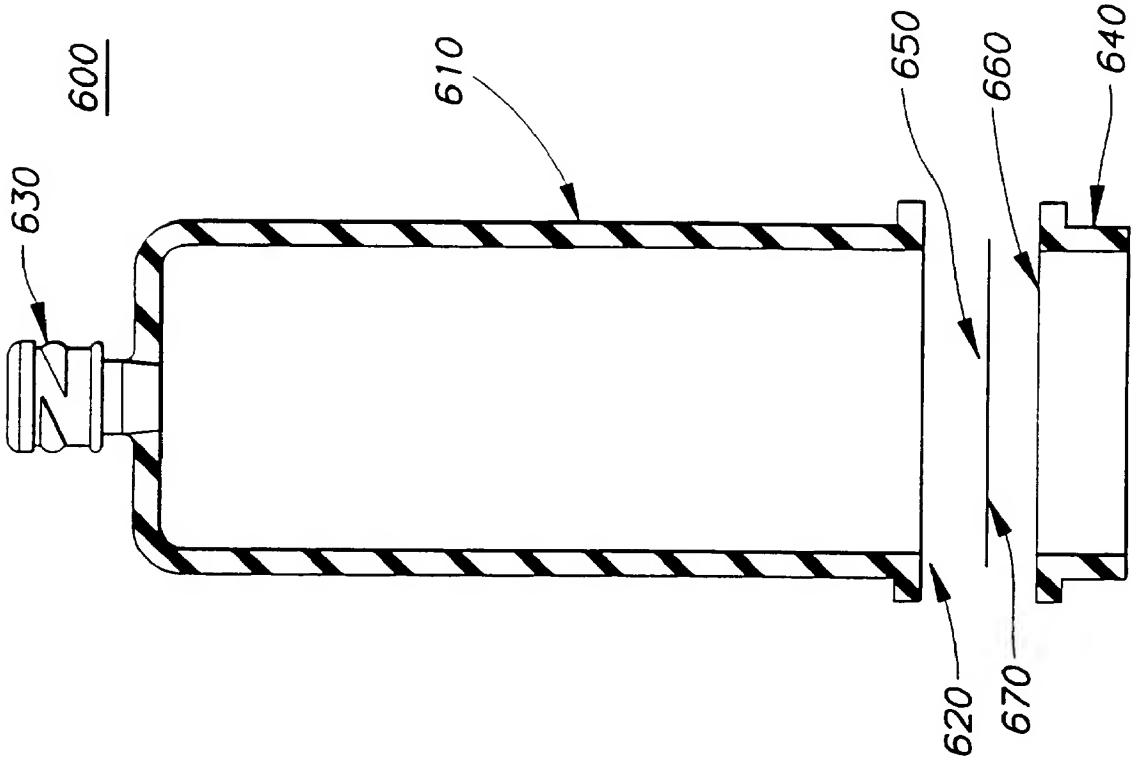


FIG. 19

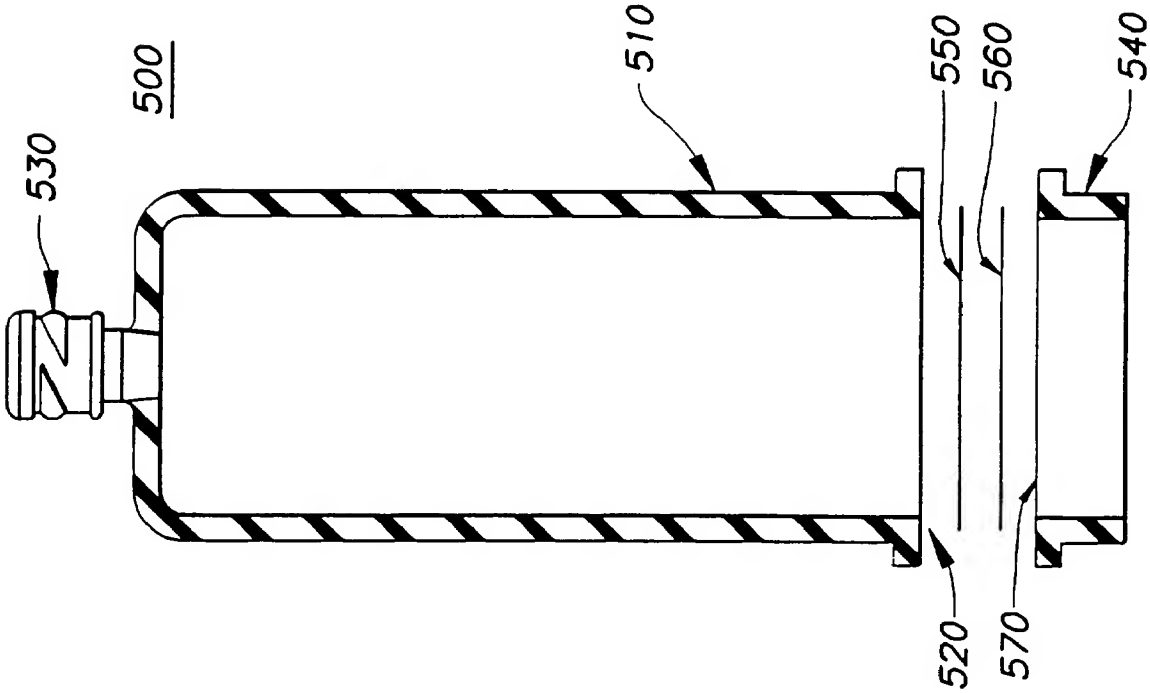


FIG. 18

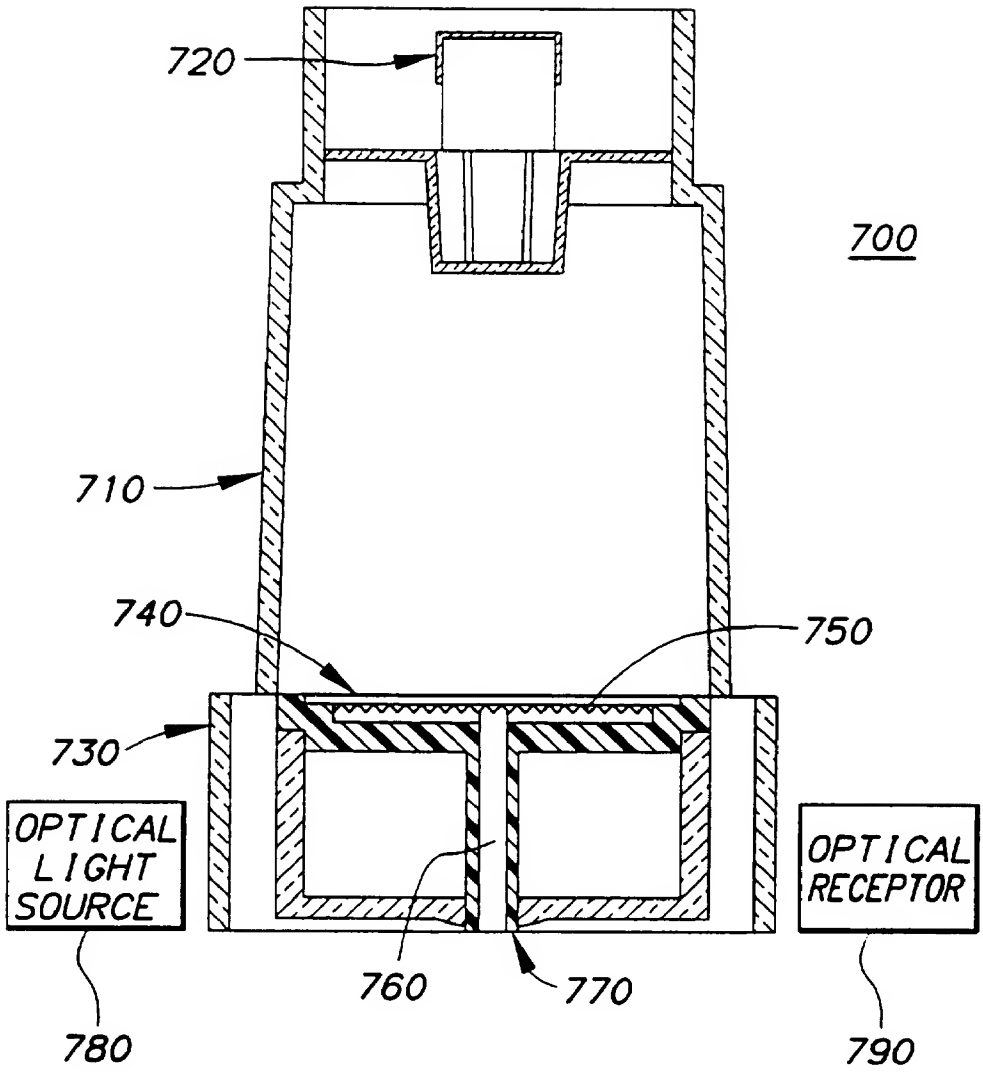

720
700
710
740
750
730
OPTICAL LIGHT SOURCE
OPTICAL RECEPTOR
760
770
780
790

FIG. 20

INTERNATIONAL SEARCH REPORT

Intl Application No
PCT/US 96/00631

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 G01N33/49 G01N33/72 B01D61/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO,A,91 08782 (PROVIDO AB) 27 June 1991 see page 1, line 12 - line 29 see page 6, line 19 - page 7, line 16	1
X	see page 12, line 1 - line 24; figure 2 see page 4, line 11 - page 15	1
A	see page 5, line 12 - line 18 ---	8,15
Y	EP,A,0 552 014 (THERAKOS) 21 July 1993 see column 1, line 30 - line 47 see column 2, line 34 - column 3, line 37 see column 5 - column 6; figures ---	1,16
Y	EP,A,0 315 252 (AKZO) 10 May 1989 see column 5, line 22 - line 48; figures ---	1,16
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search
29 May 1996

Date of mailing of the international search report
05. 06. 96

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 96/00631

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP,A,0 184 852 (BECTON) 18 June 1986 see page 6, line 16 - line 32 see page 10, line 9 - page 11, line 6; figure 6	1
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